Ambry Genetics®
A Konica Minolta Company

Copy Number Variation (CNV) Classification Scheme AUGUST 2020

CLARITY TO BETTER INFORM YOUR DECISIONS

CLASSIFICATION	
Pathogenic	1A; 4Bs; 3Bs and 2Cs
Variant, Likely Pathogenic	3Bs; 2Bs and 1C; 1B and 3Cs
Variant, Unknown Significance	Conflicting or insufficient evidence
Variant, Likely Benign	1D; 2Es
Benign	1F; 2Ds; 1D and 2Es; 4Es

CATEGORY	CRITERIA	WEIGHT
A	CNVs with ≥ 100 genes	1A
	Well-established microdeletion/duplication syndromes	1A
	CNV containing a single gene deletion (frameshift, or whole gene) with established clinical validity for autosomal dominant (AD)/X-linked (XL) disease, haploinsufficiency established as mechanism of disease	1A
	Duplication containing a single gene with established clinical validity for AD/XL disease* and established triplosensitivity (TS); (the TS gene or minimal critical region is fully contained within the observed copy number gain)	1A
B	Deletions with ≥35 coding genes	2B
	Duplications with ≥ 50 coding genes	2B
	CNV containing a single gene deletion (frameshift, or whole gene) with established clinical validity for AD/XL disease, haploinsufficiency **not** established as mechanism of disease*	1B
	Described in ≥5 probands, internal cases or case reports, with overlapping CNV region and overlapping clinical phenotype	1B-2B
	Significant disease association in one appropriately sized case-control study. OR>1.5 and p<0.05 when n>1000 case and control chromosomes across studies (Lower CI ≥1.5)	1C-3B
	Good segregation with disease 1B = 5-6 meioses; 2B = >7 meioses	1B-2B
	Confirmed or assumed *de novo* alteration	1C-3B
C	Deletions with ≥25-49 total number of unique genes	1C
	Duplications with ≥35-74 total number of unique genes	1C
	Moderate segregation with disease (at least 3-4 informative meioses) for rare diseases	1C
	CNV absent from population databases and internal database, rarity	1C
VUS	Conflicting or insufficient evidence	
D	Large case-control studies show no significant disease association	1E-1D
	Specific phenotype and lack of co-segregation in family study: Not identified in another affected family member with consistent, specific, well-defined phenotype	1E-1D
	Specific phenotype and lack of co-segregation in family study: Identified in unaffected family member and specific, well-defined phenotype observed in the proband	1E-1D
E	Described in at least 1 Database of Genomic Variants (DGV) gold standard study OR 2 studies in DGV with frequency 0.5% - 0.99% of the population (n≥100)**	1E
F	Described in at least 1 DGV gold standard study OR 2 studies in DGV with frequency ≥1% of the population (n≥100)**	1F

** If partial deletion see pathogenic criterion (PVS1) for predicted loss of function variants*
*** Does not apply for AR diseases*

MKT-0256_v3 | 08.12.20

7 Argonaut, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 ambrygen.com